FORM PTO-1390 (REV 10-95)

U S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. §371

ATTORNEY'S DOCKET NUMBER: JENA 3

U S APPLICATION NO. (If known, see 37 CFR §1 5): 09/719221

INTERNATIONAL APPLICATION NO	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/DE99/01652	7 JUNE 1999	9 JUNE 1998

TITLE OF INVENTION

PHARMACEUTICAL COMBINATIONS FOR COMPENSATING FOR A TESTOSTERONE DEFICIENCY IN MEN WHILE SIMULTANEOUSLY PROTECTING THE PROSTATE

APPLICANT(S) FOR DO/EO/US

HÜBLER, Doris, et al.

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ■ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. §371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. §371.
3. ☐ This express request to begin national examination procedures (35 U.S.C. §371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. §371(b) and PCT Articles 22 and 39(1).
4. ■ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ■ A copy of the International Application as filed (35 U.S.C. §371(c)(2))
   a. ☐ is transmitted herewith (required only if not transmitted by the International Bureau).
   b ■ has been transmitted by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ■ A translation of the International Application into English (35 U.S.C. §371(c)(2)).
7. ■ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. §371(c)(3))
   a ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ have been transmitted by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ■ have not been made and will not be made.
8. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. §371(c)(3)).
9. ☐ An oath or declaration of the inventor(s) (35 U.S.C. §371(c)(4)).
10. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. §371(c)(5)).

Items 11. to 16. below concern document(s) or information included:

11. ☐ An Information Disclosure Statement under 37 C.F.R. §§1.97 and 1.98.
12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 C.F.R. §§3.28 and 3 31 is included.
13. ■ A FIRST preliminary amendment
    ☐ A SECOND or SUBSEQUENT preliminary amendment.
14. ☐ A substitute specification.
15. ☐ A change of power of attorney and/or address letter.
16. ☐ Other items or information:

U.S. APPLICATION NO. (if known, see 37 CFR §1 5)	INTERNATIONAL APPLICATION NO	ATTORNEY'S DOCKET NUMBER
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17. ☒ The following fees are submitted:

	CALCULATIONS PTO USE ONLY
BASIC NATIONAL FEE (37 CFR §1.492 (a) (1) - (5)):	
Search Report has been prepared by the EPO or JPO..... $860.00	
International preliminary examination fee paid to USPTO (37 CFR §1.482)..... $690.00	
No international preliminary examination fee paid to USPTO (37 CFR §1.482) but international search fee paid to USPTO (37 CFR §1.445(a)(2))..... $710.00	
Neither international preliminary examination fee (37 CFR §1.482) nor international search fee (37 CFR §1.445(a)(2)) paid to USPTO..... $1000.00	
International preliminary examination fee paid to USPTO (37 CFR §1.482) and all claims satisfied provisions of PCT Article 33(2)-(4).. $100 00	
ENTER APPROPRIATE BASIC FEE AMOUNT =	$860.00
Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 C.F.R. §1.492(e)).	

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE	
Total claims	12 - 20 =	0	x $ 18.00	$0.00
Independent claims	1 - 3 =	0	x $ 80.00	$0.00
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ $ 270.00	
TOTAL OF ABOVE CALCULATIONS =				$860.00
Reduction of 1/2 for filing by small entity, if applicable. A Verified Small Entity Statement must also be filed (Note 37 C.F.R. §§1.9, 1.27, 1.28).				
SUBTOTAL =				$860.00
Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 C.F.R. §1.492(f)).				
TOTAL NATIONAL FEE =				$860.00
Fee for recording the enclosed assignment (37 C.F.R. §1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 C.F.R. §§3.28, 3.31). $40.00 per property.				
TOTAL FEES ENCLOSED =				$860.00
			Amount to be refunded:	
			charged:	

a. ■ A check in the amount of $860.00 to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account No. 13-3402 in the amount of $ _____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ■ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 13-3402. A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 C.F.R. §§1.494 or 1.495 has not been met, a petition to revive (37 C.F.R. §1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO

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AJZ:jmm

23599
PATENT TRADEMARK OFFICE

SIGNATURE

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NAME

27,969
REGISTRATION NUMBER

IN THE UNITED STATES DESIGNATED/ELECTED OFFICE

International Application No.	:	PCT/DE99/01652
International Filing Date	:	7 JUNE 1999
Priority Date(s) Claimed	:	9 JUNE 1998
Applicant(s) (DO/EO/US)	:	HÜBLER, Doris, et al.

Title: PHARMACEUTICAL COMBINATIONS FOR COMPENSATING FOR A TESTOSTERONE DEFICIENCY IN ME WHILE SIMULTANEOUSLY PROTECTING THE PROSTATE

PRELIMINARY AMENDMENT

Commissioner for Patents
Washington, D.C. 20231

SIR:

Prior to calculating the national fee, and prior to examination in the National Phase of the above-identified International application, please amend as follows:

IN THE CLAIMS:

Claim 12, lines 1 and 2, delete "at least one of claims 1 to 4" and insert --claim 1--.

REMARKS

The purpose of this Preliminary Amendment is to eliminate multiple dependent claims in order to avoid the additional fee. Applicants reserve the right to reintroduce claims to canceled combined subject matter.

Respectfully submitted,

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AJZ:jmm

Pharmaceutical Combinations for Compensating for a Testosterone Deficiency in Men While Simultaneously Protecting the Prostate

The invention relates to pharmaceutical combinations for compensating for an absolute and relative testosterone deficiency in men with simultaneous prophylaxis for the development of a benign prostatic hyperplasia (BPH) or prostate cancer that contains a natural or synthetic androgen in combination with a gestagen, an antigestagen, an antiestrogen, a GnRH analog, a testosterone-5α-reductase inhibitor, an α-andreno-receptor blocker or a phosphodiesterase inhibitor.

Various endocrine functions vary during the course of the aging process.

The normal aging process in men is accompanied by a reduction in the testicular function, especially a reduction in the serum-testosterone level.

The serum-testosterone secretion is responsible for the secondary sex characteristics, libido and potency and also has an effect on the emotional and intellectual capabilities, on the erythropoiesis, bone metabolism, protein anabolism and muscle mass, fat distribution and certain CNS functions. In lowering the serum-testosterone level, a reduction of the libido and potency, as well as fatigue, reduction of the muscle mass, osteoporosis, hot flashes, profuse sweating and slight anemia can clinically occur.

An important role is ascribed to androgens for the development and manifestations of both benign prostatic hyperplasia (BPH) and prostate cancer, however.

At older ages, diseases of the prostate occur in clusters. In 50% of men over 50 years old, this leads to a non-malignant growth of the prostate (BPH).

Hypogonadal males or castrated males never develop a BPH. Geller, J.: Androgen Inhibition and BPH. in: Bhasin et al. (Editors): Pharmacology, Biology and Clinical Applications of Androgens. John Wiley, New York (1996).

In men with and without BPH, however, no differences in androgen concentrations in the serum exist [Lee, C., Prostate 6 Supple., 52-56 (1996), Levine, A. C. Trends Endocrinol. Metab. 6, 128-132 (1995); Serio, M. and Fiorelli, G. Mol. Cell. Endocrinol. 78, C77-C81 (1991), Cunningham, G. R.: Overview of Androgens on the Normal and Abnormal Prostate. In: Bhasin et al. (Editors). Pharmacology, Biology, and Clinical Applications of Androgens. John Wiley, New York (1996)], so that obviously the cellular metabolism of testosterone into 5α-dihydrotestosterone (DHT) and estradiol in the prostate, together with local growth factors, is of decisive importance for the development both of benign prostatic hyperplasia (BPH) and prostate cancer.

Both in men over 50 and in younger men with various chronic diseases and continuous stress, all indicated clinical symptoms in serum-testosterone levels demonstrably occur in clusters even at the lower standard limits of 12.0 to 15 nmol/l.

It is known from the literature or patent literature to treat androgen-dependent systemic diseases, such as, for example, the BHP and the prostate cancer, with antiandrogens by themselves -- W94/26767 A1 -- or in combination with testolactone as an aromatase inhibitor -- DE 3121152 A1 --, with testosterone-5α-reductase inhibitor by itself -- EP 0 547 691 A1; WO 95/13077 A1 -- or in combination with antiestrogens and/or aromatase inhibitors WO 91/00731 A1.

A testosterone replacement therapy without risk to the prostate is not indicated.

In the technical literature, it is shown that androgen substitution also improves physical and mental well-being as a person ages [Bagatell et al. J. Clin. Endocrin. Metab. 79: 561-567 (1994); Tenover, J. S. Endocrinology and Metabolism Clinics of North America 23: 878-892 (1994)].

The androgen substitution in older men with reduced serum-testosterone levels is still a controversial topic for a wide variety of reasons, however, and the increased risk of diseases of the prostate by overstimulation is always emphasized.

It is therefore inadvisable to undertake androgen replacement therapy in the older or prematurely aged man analogously to postmenopausal hormone substitution of the woman [Rolf, C. and E. Nieschlag: Seneszenz [Senescence] in E. Nieschlag and H. M. Behre (Editors): Andrologie - Grundlagen und Klinik der reproduktiven Gesundheit des Mannes [Andrology -- Principles and Clinical Studies of the Reproductive Health of the Man]. Springer 1996: Jackson, J. A. et al. Arch. Intern. Med.

149: 2365-2366 (1989): Jockenhövel, F. Androgensubstitution des älteren Mannes [Androgen Substitution of the Older Man]. In: Allolio and Schulte (Editors). Praktische Endokrinologie [Practical Endocrinology]. Urban & Schwarzenberg, Munich, pp. 416-419 (1996)].

Also, e.g., after an 8-month therapy of 23 men at the ages of 40-65 years with testosterone undecanoate (160 mg/day), Holmäng, S. et al. Prostate 23, 99-106 (1996) could detect a 12% increase in size of the prostate.

In studies on male contraception with testosterone enanthate, an enlargement of the prostate was found in young men under exogenic testosterone administration by means of transrectal ultrasound studies [Wu, C. W. et al. Fertility and Sterility 65, 626-636 (1996); Wallace, E. M. et al. Int. J. Androl. 16: 35-40 (1993)].

Patent DE 196 10 645 A1 describes the use of dehydroepiandrosterone in combination with aromatase inhibitors for treatment of a relative and absolute androgen deficiency in men (hypoandrogenism). Aromatase inhibitors in terms of this patent are all those compounds that prevent the formation of estrogens from their metabolic precursors (here DHEA) by inhibiting the enzyme aromatase (inhibition of the biosynthesis).

Androgen therapy with simultaneous protection of the prostate is not indicated, however.

Patent WO 97/29735 claims androgens, antiandrogens, estrogens or antiestrogens containing transdermal systems, individually or in combination, for androgen therapy in the case

of a deficiency of the testosterone level in hypogonadal men, for hormone substitution therapy in postmenopausal women and for hormonal contraception in men and in women.

Also, androgen therapy with simultaneous protection of the prostate is not indicated here.

The object of this invention is to define suitable combination preparations for compensating for an absolute and relative testosterone deficiency in men while simultaneously protecting the prostate and in this case to avoid the above-mentioned drawbacks and actions.

The object is achieved by the use according to the invention of combination preparations according to claim 1 for compensating for an absolute and relative testosterone deficiency with simultaneous therapy of the benign prostatic hyperplasia (BPH).

The use of the combination preparations according to the invention is preferably characterized in that natural androgen is one of the substances testosterone, testosterone undecanoate, dehydroepiandrosterone, dehydroepiandrosterone sulfate, testosterone propionate, testosterone enanthate, testosterone buciclate, testosterone cypionate or androstene dione, and the synthetic androgen is one of the substances 17-methyltestosterone, fluoxymesterone, danazol, mesterolone, nandrolone decanoate, nandrolone phenylpropionate, oxandrolone, oxymetholone, or stanazolol.

It has proven advantageous that the dosage of the androgen, for example of testosterone undecanoate, is 250 to 1500 mg i.m. every 4 to 14 weeks.

In this case, the administration of 1000 mg of testosterone undecanoate every 9 to 10 weeks is especially advantageous.

The use according to the invention of combination preparations is preferably characterized in that the gestagen component is one of the substances dienogest, levonorgestrel, gestodene, desogestrel, norgestimate, norethisterone, norethisterone acetate, levonorgestrel or progesterone, chloromadinone acetate, cyproterone acetate, medroxy progesterone acetate, megestrol acetate, dydrogesterone, trimegestone or nomegestrol.

In this case, it is advantageous that the dosage of the gestagen is 20 μg to 20 mg.

The antigestagen component is preferably

4-[17ß-Hydroxy-17α-(methoxymethyl)-3oxoestra-4,9-dien-11ß-yl]benzaldehyde-1(E)-oxime (J 912);

4-[-17ß-methoxy-17α-(methoxymethyl)-3-oxo-estra-4,9-dien-11ß-yl]-benzaldehyde-1(E)-{O-[(ethylthio)carbonyl]}-oxime (J 1042);

4-[9α,10α-epoxy-17ß-hydroxy-17α-(methoxymethyl)-3-oxo-estr-4-en-11ß-yl]-benzaldehyde-1(E)-oxime (J 1116);

4-[17ß-methoxy-17α-(methoxymethyl)-3oxoestra-4,9-dien-11ß-yl]benzaldehyde-1(E)-oxime (J 867);

4-[17ß-hydroxy-17α-(methoxymethyl)-3oxoestra-4,9-dien-11ß-yl]benzaldehyde-1(E)-{O-[(N-ethyl)-carbonyl]}-oxime (J 956);

11ß-[(4-N,N-dimethylamino)-phenyl]-17ß-hydroxy-17α-propinyl-estra-4,9-dien-3-one (RU 38 486 - mifepristone);

11ß-][(4-N,N-dimethylamino)-phenyl]-17α-hydroxy-17ß-(3-hydroxypropyl-13α-methyl-gona-4,9-dien-3-one (ZK 98299 - onapristone);

11ß-(4-acetylphenyl)-17ß-hydroxy-17α-propinyl-estra-4,9-dien-3-one (ZK 112993);

11ß-[(4-N,N-dimethylamino)-phenyl]-17ß-hydroxy-17α-(3-hydroxy-1-(Z)-propenyl)-estra-4,9-dien-3-one (ZK 98 734 - lilopristone);

11ß-[(4-N,N-dimethylamino)-phenyl]-17ß-hydroxy-17α-(3-hydroxy-1-(Z)-propenyl)-estra-4-en-3-one (ZK 137 316);

11ß-[(4-N,N-dimethylamino)-phenyl]-6ß-methyl-4',5'dihydrospiro-[estra-4,9-diene-17,2'(3'H)-furan]-3-one (ORG 31 710);

11ß-[(4-N,N-dimethylamino)-phenyl]-7ß-methyl-4',5'dihydrospiro-[estra-4,9-diene-17,2'(3'H)-furan]-3-one (ORG 31 806);

11ß-(4-acetylphenyl)-(3'E)-ethylidene-4',5'dihydrospiro-[estra-4,9-diene-17,2'(3'H)-furan]-3-one (ORG 33 628).

The antiestrogen component is preferably tamoxifen, raloxifene, panomifene, toremifene, iproxifene or idoxifene.

The GnRH-analog component is preferably buserelin, goserelin, nafarelin, triptorelin or deslorelin, leuprolide or leuprolide acetate.

The testosterone-5α-reductase-inhibitor component is preferably finasteride, epristeride, permixon, or turosteride.

The α-andreno-receptor-blocker component is preferably tolazoline, phentolamine, phenoxybenzamine, alfuzosin, or prazosin.

The phosphodiesterase-inhibitor component is preferably amrinone, milrinone, trapidil, papaverine, vesnarinone or sildenafil.

The object is achieved according to the invention by use of the combinations in different preparation or administration forms.

The pharmaceutical preparation forms can depict the combinations as a uniform form or else contain two separate formulations. In this case, they can be preparations for peroral use, e.g., tablets, capsules and coated tablets; percutaneous preparation forms, e.g., transdermal therapeutic systems (TTS) or gels, sprays or ointments; intranasal preparation forms, such as nasal spray or nose drops, rectal preparation forms such as suppositories and preparations for parenteral use, e.g., implants, pressed parts and ampoules.

The preparation forms are produced in a way that is known in the art with use of commonly used adjuvants and vehicles, as are described in, for example, "Remington's Pharmaceutical Sciences Handbook, Hack Pub. Co., N.Y., USA."

A pharmaceutical combination for compensating for an absolute and relative testosterone deficiency in men with simultaneous prophylaxis of benign prostatic hyperplasia (BPH) was found.

In comparison to the combination according to the invention, any active ingredient by itself cannot achieve the desired goal to this extent and only with significant side effects.

With the combinations according to the invention, the DHT-stimulation that is caused by the administration of the androgens or overstimulation in the prostate is compensated for by the indicated components, such as gestagens, antigestagens, antiestrogens, GnRH-analogs, testosterone-5α-reductase inhibitors, α-andreno-receptor blockers or phosphodiesterase inhibitors.

In the example of the inhibition of the androgen-dependent cell proliferation in LNCaP prostate cells, the biological mechanism of action of the combination of 17ß-hydroxy-17α-methyl-estra-4,9,11-trien-3-one (R 1881) + the 17α-cyano-methyl-17ß-hydroxy-estra-4,9-dien-3-one (DIENOGEST = DNG) was examined.

To this end, the human prostate cancer cell LNCaP was cultivated under routine conditions in Dulbecco's modified Eagle medium (DMEM) with the addition of 10% FCS (fetal calf serum).

The cells were then cultured for 2 to 6 passages with DMEM and 10% DCC-FCS (steroid-depleted FCS), before it was used in a growth assay with 5% DCC-FCS.

For the test, the cells were saturated in 24-well plates (10,000 cells/well and ml).

After 24 hours, the steroids that were dissolved in ethanol were added to fresh test medium (final concentration of ethanol 0.1%), and the cells were incubated for 7 days at 37° (5% CO_2).

The cell number was determined after this time in a cell counting and analysis system (CASY, Schärfe System GmbH).

It can be seen from Figure 1 that the very strong androgen 17ß-hydroxy-17α-methyl-estra-4,9,11-trien-3-one (R1881) induces a cell growth. Based on the dose of the second component -- here the gestagen DNG -- however, the androgen-dependent cell proliferation of the prostate-cancer-cell line is inhibited. The dienogest action is first and foremost peripheral to the sex organs (Oettel, M. et al., Der Einfluß einer Ethinylestradiol-Dienogest-Kombination auf die Serum-Androgen-Konzentrationen [The Effect of an Ethinylestradiol-Dienogest-Combination on the Serum-Androgen-Concentrations], Zentralblatt Gynäkol 119, 597-606, 1997).

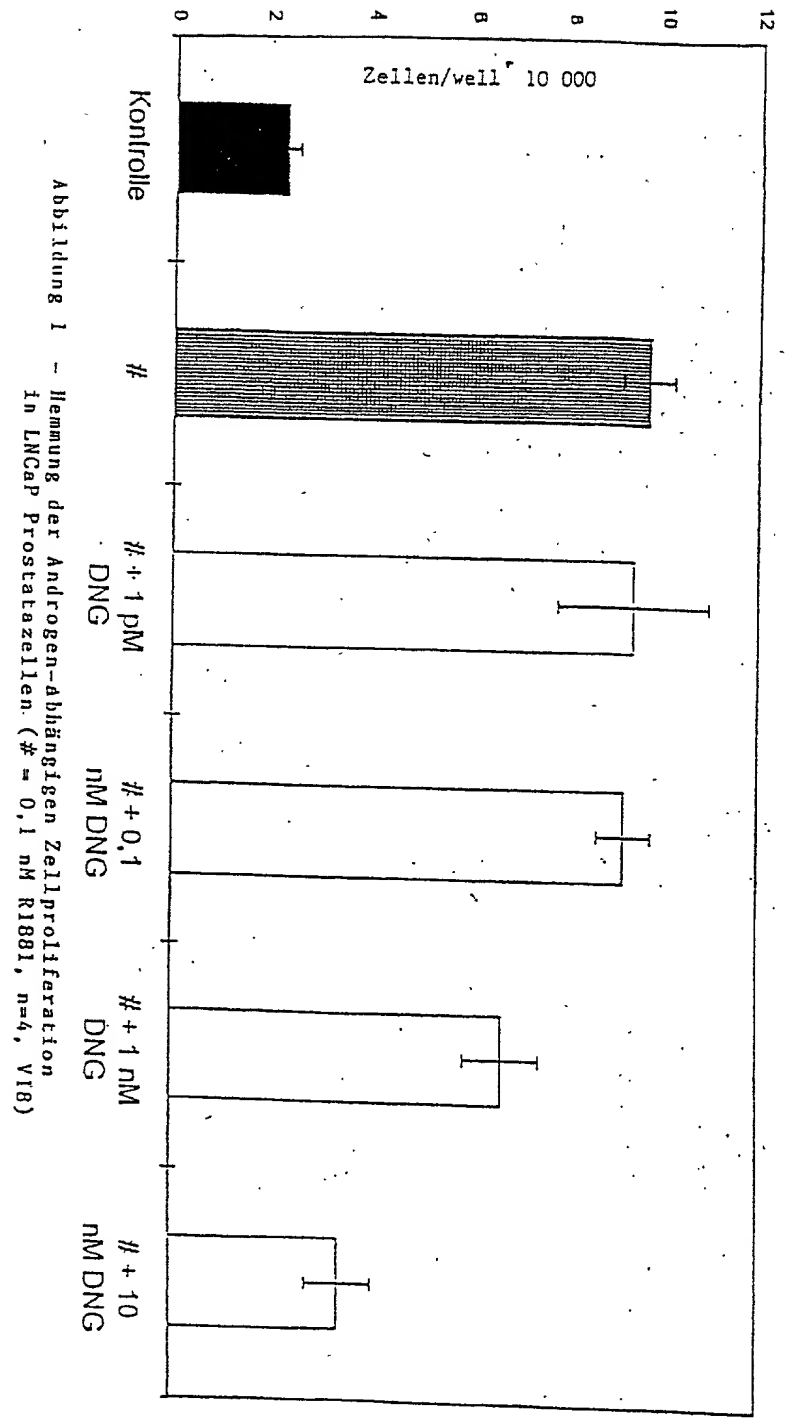

Abbildung 1 - Hemmung der Androgen-abhängigen Zellproliferation in LNCaP Prostatazellen (# = 0,1 nM R1881, n=4, V18)

[Key to Table:]
Zellen/well = Cells/well
Kontrolle = Control

Figure 1 -- Inhibition of the Androgen-dependent Cell Proliferation in LNCaP Prostate Cells (# = 0.1 nM R1881, n = 4, V18)

The inhibition of a prostate growth that was induced by androgens and that was treated with a combination according to the invention, was also examined in the animal experiment.

To this end, 5 male NMRI mice of Møllegaard Breeding Centre Deutschland GmbH, Schönwalde weighing 28-30 g were castrated. Two weeks after the castration, testosterone propionate (TP) by itself -- 0.1 mg/animal -- was administered to the control animals.

Also, two weeks after castration, the test animals were orally treated daily for one week with testosterone propionate (TP) 0.1 mg/animal/day s.c. and simultaneously with the following gestagens and the following dosages:

cyproterone acetate (CPA) at dosages of 0.1; 0.3; 1; 3 mg/animal/day

dienogest (DNG) at dosages of 0.3; 1; 3; 10 mg/animal/day,

chloromadinone acetate (CMA) at dosages 0.3; 1; 3; 10 mg/animal/day.

At the end of the test, the prostate weights of the mice were determined, and the test groups were compared.

In Table 1, the determined prostate weights of the treated mice are indicated during the course of the test.

Prostate Weights of Castrated Mice in mg (Mean Value ± S.D.) after Combined Testosterone/Gestagen Treatment (n = 5 animals/group)						
Gestagen dosage ./. groupings		0.1 (mg/an-imal/ day)	0.3 (mg/an-imal/ day)	1.0 (mg/an-imal/ day)	3.0 (mg/an-imal/ day)	10.0 (mg/an-imal/ day)
Intact control	3.0 ± 0.8					
Castrated control	1.7 ± 0.7					
TP control	4.4 ± 0.7					
TP + CPA		2.7± 1.2*	3.3±1.3	2.2±1.1 *	2.3±0.8 *	2.7±0.7 *
TP + DNG			2.7±0.7 *	3.4±0.5 *	3.1±0.7 *	2.4±0.9 *
TP + CMA			3.0±1.0 *	3.3±0.8	3.0±1.1 *	2.5±0.4 *
* significant p ≥ 0.05 (substance group vs. TP)						

From Table 1, it can be seen that the selected pure testosterone dose -- 0.1 mg/animal/day -- causes a clear increase of the prostate weight compared to the castrated and the intact control animals. The androgen/gestagen combination reduces the androgen-produced increase of the prostate weight -- depending on the dosage of the gestagen -- up to the range of prostate weights of intact comparison animals.

Thus, the compensating for the relative testosterone deficiency and the simultaneous protection of the prostate is demonstrably ensured.

With the combinations according to the invention, pharmaceutical agents are made available that compensate for a relative testosterone deficiency in men and simultaneously protect the prostate.

Claims

1. Use of combination preparations that contain

-- a natural or synthetic androgen

-- and a component from the group of gestagens, antigestagens, antiestrogens, GnRH analogs, testosterone-5α-reductase inhibitors, α-andreno-receptor blockers or phosphodiesterase inhibitors

for compensating for an absolute or relative testosterone deficiency with simultaneous prophylaxis for the development of a benign prostatic hyperplasia (BPH) or a prostate cancer.

2. Use of combination preparations according to claim 1, characterized in that the natural androgen component is testosterone, testosterone testosterone undecanoate, dehydroepiandrosterone, dehydroepiandrosterone sulfate, testosterone propionate, testosterone enanthate, testosterone buciclate, testosterone cypionate or androstene dione.

3. Use of combination preparations according to claim 1, wherein the synthetic androgen component is 17-methyltestosterone, fluoxymesterone, danazol, mesterolone, nandrolone decanoate, nandrolone phenylpropionate, oxandrolone, oxymetholone, or stanazolol.

4. Use of combination preparations according to claim 1, wherein the gestagen component is dienogest, levonorgestrel, gestodene, desogestrel, norgestimate, norethisterone, norethisterone acetate, levonorgestrel or progesterone, chloromadinone acetate, cyproterone acetate, medroxy progesterone

acetate, megestrol acetate, dydrogesterone, trimegestone or nomegestrol.

5. Use of the combination preparations according to claim 1, wherein the antigestagen component is

4-[17ß-Hydroxy-17α-(methoxymethyl)-3oxoestra-4,9-dien-11ß-yl]benzaldehyde-1(E)-oxime (J 912);

4-[-17ß-methoxy-17α-(methoxymethyl)-3-oxo-estra-4,9-dien-11ß-yl]-benzaldehyde-1(E)-{O-[(ethylthio)carbonyl]}-oxime (J 1042);

4-[9α,10α-epoxy-17ß-hydroxy-17α-(methoxymethyl)-3-oxo-estr-4-en-11ß-yl]-benzaldehyde-1(E)-oxime (J 1116);

4-[17ß-methoxy-17α-(methoxymethyl)-3oxoestra-4,9-dien-11ß-yl]benzaldehyde-1(E)-oxime (J 867);

4-[17ß-hydroxy-17α-(methoxymethyl)-3oxoestra-4,9-dien-11ß-yl]benzaldehyde-1(E)-{O-[(N-ethyl)-carbonyl]}-oxime (J 956);

11ß-[(4-N,N-dimethylamino)-phenyl]-17ß-hydroxy-17α-propinyl-estra-4,9-dien-3-one (RU 38 486 - mifepristone);

11ß-][(4-N,N-dimethylamino)-phenyl]-17α-hydroxy-17ß-(3-hydroxypropyl-13α-methyl-gona-4,9-dien-3-one (ZK 98299 - onapristone);

11ß-(4-acetylphenyl)-17ß-hydroxy-17α-propinyl-estra-4,9-dien-3-one (ZK 112993);

11ß-[(4-N,N-dimethylamino)-phenyl]-17ß-hydroxy-17α-(3-hydroxy-1-(Z)-propenyl)-estra-4,9-dien-3-one (ZK 98 734 - lilopristone);

11ß-[(4-N,N-dimethylamino)-phenyl]-17ß-hydroxy-17α-(3-hydroxy-1-(Z)-propenyl)-estra-4-en-3-one (ZK 137 316);

11ß-[(4-N,N-dimethylamino)-phenyl]-6ß-methyl-4',5'dihydrospiro-[estra-4,9-diene-17,2'(3'H)-furan]-3-one (ORG 31 710);

11ß-[(4-N,N-dimethylamino)-phenyl]-7ß-methyl-4',5'dihydrospiro-[estra-4,9-diene-17,2'(3'H)-furan]-3-one (ORG 31 806);

11ß-(4-acetylphenyl)-(3'E)-ethylidene-4',5'dihydrospiro-[estra-4,9-diene-17,2'(3H)-furan]-3-one (ORG 33 628).

6. Use of combination preparations according to claim 1, wherein the antiestrogen component is tamoxifen, raloxifene, panomifene, toremifene, iproxifene or idoxifene.

7. Use of combination preparations according to claim 1, wherein the GnRH-analog component is buserelin, goserelin, nafarelin, triptorelin or deslorelin, leuprolide or leuprolide acetate.

8. Use of combination preparations according to claim 1, wherein the antiestrogen component is tamoxifen, raloxifene, panomifene, toremifene, iproxifene or idoxifene.

9. Use of combination preparations according to claim 1, wherein the testosterone-5α-reductase-inhibitor component is finasteride, epristeride, permixon, or turosteride.

10. Use of combination preparations according to claim 1, wherein the α-andreno-receptor-blocker component is tolazoline, phentolamine, phenoxybenzamine, alfuzosin, or prazosin.

11. Use of combination preparations according to claim 1, wherein the phosphodiesterase-inhibitor component is amrinone, milrinone, trapidil, papaverine, vesnarinone or sildenafil.

12. Use of a combination preparation according to at least one of claims 1 to 4, wherein it is used in the form of tablets, capsules, coated tablets, transdermal therapy systems, ampoules, suppositories, gels, ointments, nose drops, implants, pressed parts or biodegradable microspheres.

Attorney Docket Number JENA-3

DECLARATION FOR PATENT APPLICATION

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

PHARMACEUTICAL COMBINATION USED TO COMPENSATE FOR A TESTOSTERONE DEFICIENCY WHILE PROTECTING THE PROSTATE

the specification of which

- ☐ is attached hereto
- ■ was filed on 7 JUNE 1999 as United States Application Number or PCT International Application Number PCT/DE99/01652 and (if applicable) was amended on _____

I hereby authorize our attorneys to insert the serial number assigned to this application.

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR §1 56

I hereby claim foreign priority benefits under 35 U.S.C. §119(a)-(d) or § 365(b) of any foreign application(s) for patent or inventor's certificate, or §365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or PCT International application having a filing date before that of the application on which priority is claimed

PRIOR FOREIGN/PCT APPLICATION(S) AND ANY PRIORITY CLAIMS UNDER 35 USC §119			
APPLICATION NO.	COUNTRY	DAY/MONTH/YEAR FILED	PRIORITY CLAIMED
198 25 591.8	Germany	09/06/1998	Yes

I hereby claim the benefit under 35 U.S C §119(e) of any United States provisional application(s) listed below

PROVISIONAL APPLICATION(S) UNDER 35 U.S.C. §119(e)	
APPLICATION NUMBER	FILING DATE

I hereby claim the benefit under 35 U.S.C. §120 of any United States application, or §365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U S.C §112.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR §1 56 which became available between the filing date of the prior application and the national or PCT International filing date of this application

PRIOR U.S./PCT INTERNATIONAL APPLICATION(S) DESIGNATED FOR BENEFIT UNDER 37 U.S.C. §120		
APPLICATION NO.	FILING DATE	STATUS — PATENTED, PENDING, ABANDONED

I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected herewith. I. William Millen (19,544); John L. White (17,746), Anthony J. Zelano (27,969), Alan E J Branigan (20,565); John R Moses (24,983), Harry B. Shubin (32,004); Brion P. Heaney (32,542), Richard J Traverso (30,595); John A. Sopp (33,103); Richard M. Lebovitz (37,067), John H Thomas (33,460); Catherine M Joyce (40,668); Nancy J Axelrod (44,014), James T. Moore (35,619); James E Ruland (40,921) and Jennifer J Branigan (37,432)

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Full Name of sole or first inventor (given name, family name) Doris Hübler	
Signature Doris Hübler	Date 16/11/2000
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Signature Michael Oertel	Date 10/12/2000
Residence Jena, Germany	Citizenship Germany
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Full Name of additional joint inventor (given name, family name) Lothar Sobek	
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Residence Jena, Germany	Citizenship Germany
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Full Name of additional joint inventor (given name, family name) Walter Elger	
Signature Walter Elger	Date 27/11/2000
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Post Office Address Schorlemer Allee 12b, D-14195, Berlin, Germany	
Full Name of additional joint inventor (given name, family name) Abdul-Abbas Al-Mudhaffar	
Signature Abdul-Abbas Al-Iwan	Date 20/11/2000
Residence Jena, Germany	Citizenship Germany
Post Office Address S -Allende-Platz 15, D-07747, Jena, Germany	

☐ Additional joint inventors are named on separately numbered sheets attached hereto

Attorney Docket Number JENA-3

DECLARATION FOR PATENT APPLICATION

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PHARMACEUTICAL COMBINATION USED TO COMPENSATE FOR A TESTOSTERONE DEFICIENCY WHILE PROTECTING THE PROSTATE

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- ☐ is attached hereto
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PRIOR FOREIGN/PCT APPLICATION(S) AND ANY PRIORITY CLAIMS UNDER 35 USC §119			
APPLICATION NO.	COUNTRY	DAY/MONTH/YEAR FILED	PRIORITY CLAIMED
198 25 591 8	Germany	09/06/1998	Yes

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PROVISIONAL APPLICATION(S) UNDER 35 U.S.C. §119(e)	
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I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR §1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application

PRIOR U.S./PCT INTERNATIONAL APPLICATION(S) DESIGNATED FOR BENEFIT UNDER 37 U.S.C. §120		
APPLICATION NO.	FILING DATE	STATUS — PATENTED, PENDING, ABANDONED

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Declaration for Patent Application (Con..... 7032436410

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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Full Name of additional joint inventor (given name, family name) Michael Oertel	
Signature	Date
Residence Jena, Germany DEX	Citizenship Germany
Post Office Address Beethovenstrasse 30, D-07743, Jena, Germany	
Full Name of additional joint inventor (given name, family name) Lothar Sobek	
Signature Lothar Sobek	Date 17/11/2000
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Signature Walter Elger	Date 27/11/2000
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Signature Abdul-Abbas Al-Mudhaffar	Date 20/11/2000
Residence Jena, Germany DEX	Citizenship Germany
Post Office Address S -Allende-Platz 15, D-07747, Jena, Germany	

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